CONDITIONAL PETITION FOR EXTENSION OF TIME

If entry and consideration of the amendments above requires an extension of time, Applicants respectfully request that this be considered a petition therefore. The Commissioner is authorized to charge any fee(s) due in this connection to Deposit Account No. 14-1263.

ADDITIONAL FEE

Please charge any insufficiency of fees, or credit any excess, to Deposit Account No. 14-1263.

REMARKS

The applicants would like to thank Examiner Borin for meeting with the applicants' representative (Howard C. Lee) for the interview of 22 July 2002. If the composition claims are not allowed prior to the forwarding of this application to the BPAI for a decision of an Appeal Brief, the applicants anticipate filing a divisional application for the method of use claims as suggested by the examiner. Should the composition claims be found to be allowable prior to receipt by the BPAI, it is requested that the method of use claims be rejoined.

Summary of Amendments Made

Claims 1, 3, 4, 5 and 7-10 have been cancelled. Claims 6 and 11-13 have been amended. Claims 14-23 have been added. Claims 6 and 11-24 are now pending. It is believed that no new matter has been added.

The specification has been amended to correct certain typographical errors which were discovered upon review:

The correction on page 11 for the terms "stearoyl" and "palmitoyl" is due to the fact that R was previously defined to be a "branched or unbranched, saturated of unsaturated hydrocarbon radical, in particular, an alkyl radical of 1 to 30 carbon atoms" (see page 9, line 8-11 of specification) and these figures were intended to represent a "particularly preferred" embodiment of this alkyl moiety. The terms "stearoyl" and "palmitoyl" accurately reflect what the ***combination*** R-C(=O) represents, but would be inaccurate for R itself.

Request for Clarification on Scope of Claims Examined

During the interview it was indicated that preparation which used oligopeptides such as those

described in claim 21 were not part of the examination. However, in the examiner's restriction requirement (Paper No. 5) it was stated on page 4, fourth from last line, that "Claims 1, 3, 4, 6 are examined on merits to the extent they read on the monomer oligopeptides VVRP, its amide and/or N-acetyl derivative." N-acetyl for the purposes of this discussion would be readable upon the variable R = CH_3, i.e. an alkyl radical of one carbon.

Claim 21 defines R to be an n-C_{15} or an n-C_{17} alkyl radical which is well within the original definition of claim 1 ("branched or unbranched saturated or unsaturated hydrocarbon radical) and the currently pending independent claim 14 ("branched or unbranched, saturated or unsaturated alkyl radical having C_1-C_{30} carbon atoms). If the scope of examination is as indicated by the examiner, what is the basis by which it is held that acylated oligopeptides with alkyl radicals on the acyl group differing only in the number of carbon atoms constitute a patentably distinct invention?

35 U.S.C. 103(a) rejections

Preliminary note: It is noted that in the previous office action, seven (7) separate 103(a) rejection were made using various combinations of references. It is respectfully requested that if the examiner maintains some form of their 103(a) rejection as it would apply to the currently pending claims, that the rejection is combined into a single rejection, i.e. If multiple references are needed to teach "all claim limitations" as stated in MPEP 2143.03, MPEP 2145 provides that "Reliance on a large number of references in a rejection does not, without more, weight against the obviousness of the claimed invention." *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). This will result in a much shorter Appeal Brief (and corresponding Examiner's Answer) should this become necessary.

In light of the amendments made to the claims above, it is presumed that should the examiner maintain his rejection(s), they would now be based on Kohmura et al. as the primary reference with some combination of Stein et al., Greene et al., Goodman and Gilman's, Cho et al., Bungaard and Sumner-Smith (i.e. the references used in paragraphs 3, 4, 6, and 9 of the examiner's previous office action). The applicants respectfully request reconsideration of any such rejection.

The applicants acknowledge that motivation in the prior art to combine references need not be identical to the applicants intended use. However, it is believed that even for the motivation of forming a cosmetic or dermatological preparation for the purpose of ACE inhibiting effect, the examiner's cited references do not render the applicants' claimed invention to be obvious for the following reasons:

Kohmura et al. reference

Kohmura et al. teaches the VVRP tetrapeptide but differs from the applicants' invention in several regards which include:

(1) There is no indication that this tetrapeptide was used in preparation form and if they were, that the preparation form was a cosmetic or dermatological topical water-in-oil preparation form for cosmetic and dermatological lightening of the skin or preventing tanning of the skin caused by UV radiation.

(2) Kohmura et al. only discloses the VVRP tetrapeptide not derivatized forms thereof such as those of (b), (c) and (d) in claim 14.

(3) The teachings of Kohmura et al. teach away from using VVRP as an ACE-inhibitor.

Kohmura et al. in view of any or all of Stein et al., Goodman and Gilman's "The Phamacological Basis of Therapeutics", Cho et al., Bundgaard and Sumner-Smith

When considering the teachings of Stein et al. as a whole, part of their teachings are directed toward topical or systemic pharmaceutical compositions which contain an ACE inhibitor ***and a novel renin inhibitor*** for the treatment or reduction of intraocular pressure (glaucoma). This differs from Kohmura et al. and the applicants' invention as the "topical" nature of their invention is directed toward ophthalmic administration not cosmetic or dermatological administration (i.e. the meaning of claims of issued patents are interpreted in light of the specification – see MPEP 2111.01)

Moreover, Stein et al. requires that an ACE inhibitor be used in conjunction with their novel renin inhibitors (see col. 22, lines 17-36) in order to reduce the side effects associated with ACE inhibitors, i.e. Stein et al. teaches away from using an ACE inhibitor alone as part of a composition.

In addition, the only direction given by Stein et al. with respect to ACE inhibitors is the use of captopril and enalapril (see col. 22, line 21 and claim 5) which are both derivatives of proline (i.e. derivatives of a single amino acid not the tetrapeptide or derivatives thereof as claimed by the applicants). If the examiner is asserting that there is equivalency for all ACE inhibitors, this has not been shown. Even if this could be shown, it was previously argued that ACE inhibitors were known in the art to occasionally produce skin rash (page 751 from Goodman and Gilman's) which represents an additional teaching away from using ACE inhibitors in cosmetic or

dermatological preparations.

Greene et al. is used to show that peptide formulations for topical treatment of ocular and skin can exist in water-in-oil emulsion form. However, Greene et al. is directed toward antibodies and their use in enhancing proliferation of an epithelial cell of the skin, i.e. both the structure of the peptides and the intended use of those peptides are far removed from the teachings of the applicants' claimed invention, the teachings of Kohmura et al. or Stein et al. and as such is unsuitable for combination. Similarly, Cho et al. only teaches that polypeptides unrelated to the previously cited references or the applicants invention could be in the form of a water-in-oil formulation for oral use.

The Bungaard and Sumner-Smith references are relied upon to show the alleged obviousness of modifying the VVRP tetrapeptide to the forms which are within the scope of tetrapeptides used by the applicants.

With respect to the Bungaard/Sumner-Smith teachings and difference (3) above, the Kohmura et al. reference stated that the most potent *in vitro* inhibitor of ACE was the oligopeptides VRP (see page 835, Table 1 and col. 2, lines 8-10 (line 1 being the first line of text after the table)) and that "Elongation of the peptide chain of Val-Arg-Pro one by one towards its N-terminus gave compounds 6-11: as the size of the peptide increased, the potency decreased." (see page 835, col. 2, lines 16-19), i.e. one of ordinary skill in the art would not be motivated to select VVRP to modify into composition form as this is a less effective agent for inhibiting ACE and would not automatically assume that modification as taught by Bungaard/Sumner-Smith would result in "at least similar effectiveness in inhibition of ACE" especially in light of Stein et al.'s teaching that ACE inhibitors possess undesired side effects when used alone.

Each of the supporting references used appears to consider selected portions of their respective teachings. However, MPEP 2141.02 makes the contingency that "A prior art reference must be considered in its entirety, i.e. as a **whole**, ***including portions that would lead away from the claimed invention.***" (see MPEP 2141.02 and *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983)). It has also been held that ***"[i]t is impermissible*** within the framework of section 103 ***to pick and choose*** from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." (see *In re Wesslau*, 353 F.2d 238, 241, 147 USPQ 391, 393 (CCPA 1965)).

Moreover, the motivation for selecting a particular teaching from the prior art appears to be based on the supposition that a particular modification to the Kohmura et al. teachings could be done. However, the motivation for making the modification does not flow from either the teachings of Kohmura et al. or the secondary references ("The mere fact that references can be combined or

modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) and MPEP 2143.01). In the present case, the prior art did not suggest the desirability of the combination; specific benefits deemed to be beneficial for the teachings of Kohmura et al. were asserted by the examiner.

CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the foregoing Amendment under 37 CFR § 1.111 (12 pages total) is being facsimile transmitted to the United States Patent and Trademark Office on the date indicated below:

Date: **29 July 2002**

By: Howard C. Lee
Howard C. Lee

CLEAN COPY OF CLAIMS SHOWING AMENDMENTS MADE

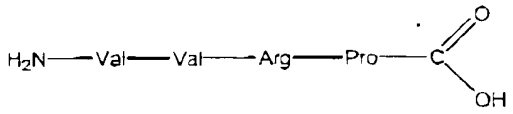
6. **[Topical water-in-oil preparations according to Claim 1]** ***The topical water-in-oil preparation of claim 14***, wherein the oligopeptides(s) is/are present in cosmetic or dermatological topical preparations in concentration of 0.000001 -10% by weight, based on the total weight of the preparations.

11. **[Topical water-in-oil preparations according to Claim 1]** ***The topical water-in-oil preparation of claim 6***, wherein the oligopeptides(s) is/are present in the cosmetic or dermatological topical preparations in concentrations of 0.0001 – 1% by weight based on the total weight of the preparations.

12. **[Topical water-in-oil preparations according to Claim 1]** ***The topical water-in-oil preparation of claim 11***, wherein the oligopeptides(s) is/are present in the cosmetic or dermatological topical preparations in concentrations of 0.0001 – 0.1% by weight based on the total weight of the preparations.

13. A method of preventing or treating undesired skin pigmentation comprising topically applying to skin an effective amount **[therefore]** of **[a]** ***the*** topical water-in-oil preparation **[according to claim 1]** ***of any one of claims 14-20***.

14. A cosmetic or dermatological topical water-in-oil preparation for cosmetic and topical dermatological lightening of the skin or preventing tanning of the skin caused by UV radiation which comprises of one or more monomeric oligopeptides selected from the group consisting of:

(a) 

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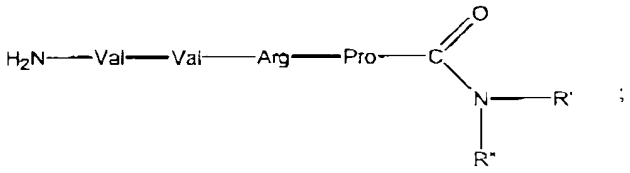
(b) 

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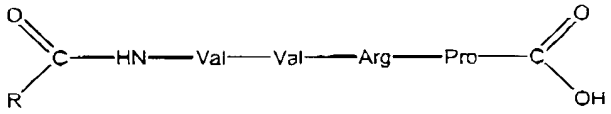
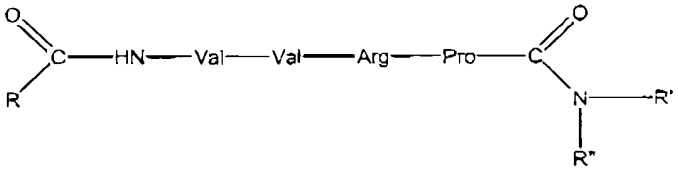
(c) 

; and

(d) 

,

wherein:

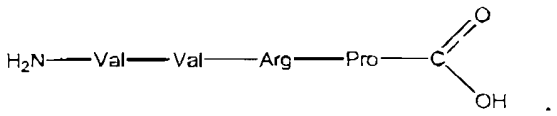
R represents a branched or unbranched, saturated or unsaturated alkyl radical having C_1-C_{30} carbon atoms,

R' and R" independently of one another may be selected from the group consisting of hydrogen and branched or unbranched, saturated of unsaturated alkyl radical having C_1-C_{30} carbon atoms,

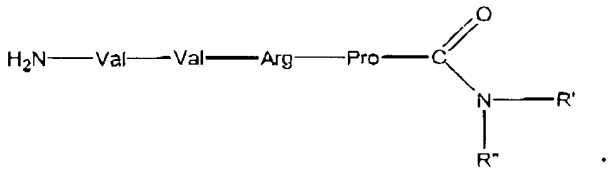
one or more cosmetically or dermatologically acceptable active ingredients, auxiliaries and/or additives; and

a cosmetically or dermatologically acceptable carrier.

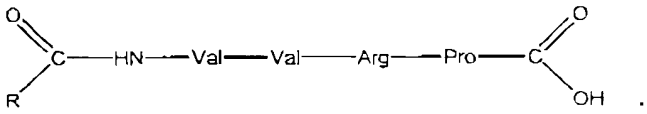
15. The cosmetic or dermatological topical water-in-oil preparation of claim 14 wherein the oligopeptide is

(a) 

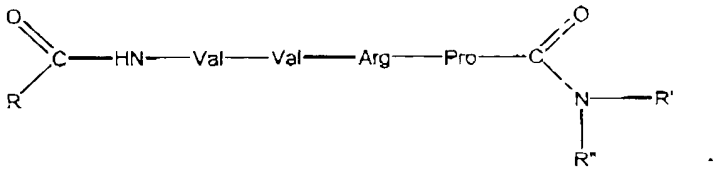
16. The cosmetic or dermatological topical water-in-oil preparation of claim 14 wherein the oligopeptide is

(b) 

17. The cosmetic or dermatological topical water-in-oil preparation of claim 14 wherein the oligopeptide is

(c) 

18. The cosmetic or dermatological topical water-in-oil preparation of claim 14 wherein the oligopeptide is

(d) 

19. The cosmetic or dermatological topical water-in-oil preparation of claim 16 wherein R'

and R" is hydrogen.

20. The cosmetic or dermatological topical water-in-oil preparation of claim 17 wherein R is methyl.

21. The cosmetic or dermatological topical water-in-oil preparation of claim 17 wherein R is an n-C_{15} or n-C_{17} alkyl radical.

22. The cosmetic of dermatological topical water-in-oil preparation of claim 18 wherein R is methyl, R' is hydrogen and R" is hydrogen.

23. The method of preventing or treating undesired skin pigmentation comprising topically applying to skin an effective amount of the topical water-in-oil preparation of claim 19.

24. The method of preventing or treating undesired skin pigmentation comprising topically applying to skin an effective amount of the topical water-in-oil preparation of claim 20.

25. The method of preventing or treating undesired skin pigmentation comprising topically applying to skin an effective amount of the topical water-in-oil preparation of any one of claim 21.

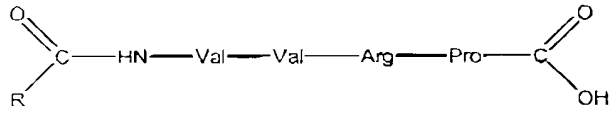
26. The method of preventing or treating undesired skin pigmentation comprising topically applying to skin an effective amount of the topical water-in-oil preparation of any one of claim 22.

Copy of Amendment Made to Specification

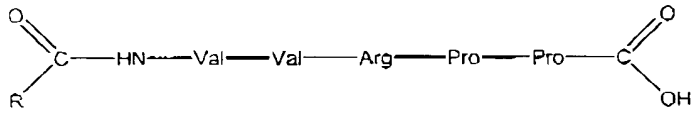
are acylated on the N-terminus and/or amidated on the C-terminus.

Preferred acylated oligopeptides are those which are acylated on the N-terminus with unbranched alkanoyl groups.

Particularly preferred are



and



R representing [the **stearoyl**] ***n*-C_{15}** or [the **palmitoyl**] ***n*-C_{17}** radical.

It may be preferable to synthesize the peptides of the present invention using recombinant DNA methods. Alternatively, it may be preferable to synthesize the peptides of the present invention using the well-known chain elongation techniques such as solid-phase synthesis, as on a Merrifield resin or the like.

To synthesize a peptide using recombinant DNA, one typically synthesizes a double-stranded DNA chain which encodes the desired amino acid sequence. The degeneracy of the genetic code permits a wide variety of codon combinations to be used to form the DNA chain that encodes the product peptide. Certain particular codons are more efficient for peptide expression in certain types of organisms and the selection of codons preferably is made according to those codons which are most efficient for expression in the type of organism which is to serve as the host for the recombinant vector. However, any correct set of codons should encode the desired product, even if slightly less effi-